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A CASE OF ATYPICAL MYELOID LEUKÆMIA WITH NODULAR INFILTRATION OF THE SKIN.*

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The patient, R. C—, a widow, aged 58 years, came to the Skin-Department of St. George's Hospital on March 17th, 1909, complaining of "lumps in the skin," which she had first noticed two months previously. She stated that for several months before this she had noticed pains in her bones from time to time, particularly the breast bone, and also in the small of her back and ribs. Otherwise she had not had any illness which appeared to bear on her present condition.

The nodules first appeared on the lower part of the abdomen, and rapidly spread over the front of the body. Each individual nodule was at first small, about the size of a pea, and grew in the course of a few days to the size of a large raisin. When the nodules first appeared they were much darker than at present, in fact, almost black; they did not cause any itching or pain. She was fairly well in herself, only rather weak. She had lost about a stone in weight in the last two months.

* A drawing of the case was shown at the Dermatological Section of the Royal Society of Medicine on June 17th, 1909 (*vide Brit. Journ. Derm.*, London, 1909, vol. xxi, p. 259).

On examination the patient was seen to be a very pale, rather shrunken woman, the skin having a transparent look, but not lemon-coloured. The nodules were of a grey-slate colour for the most part, but some of the larger ones were plum-coloured, not unlike in shape, colour, and size a half damson. The skin over them was shiny, smooth, free from scales, and not umbilicated. They were oval in shape, the long axis of the ovoid tending to run obliquely across the body, especially in the lower part of the abdomen. The distribution was roughly symmetrical. They were firm to touch, very superficial, in the true skin rather than in the subcutaneous tissue; some of them were a little tender.

The nodules, as will be noted in the photograph (Plate), were distributed thickly over the front of the trunk; above the pubes, and to a less extent at the top of the sternum (not shown in the photograph); they were so near together as to be confluent in places. There were very few on the back, one or two groups on the internal surface of both thighs, and some isolated nodules on the calves and upper arms. There were none on the head and neck, or on the mucous membranes as far as could be seen. Enlarged glands could be felt in the axillæ and groins; they were soft and freely movable. The spleen was shown to be enlarged on percussion, dulness extending upwards to the eighth rib in the anterior axillary line, but on admission to the hospital it could not be felt below the costal margin. A few days afterwards, however, it could be detected on deep inspiration, and steadily increased in size. There was nothing else abnormal detected in either the abdominal or thoracic organs. The teeth showed several carious stumps, but there was no marked degree of pyorrhœa and no stomatitis.

The general aspect of the case suggested the provisional diagnosis of multiple pigmented sarcoma, but the possibility of leukæmia was raised before the result of a biopsy established the presence of leukæmia. The biopsy was kindly carried out by Mr. Fraukau, who removed a nodule from the abdominal wall under a local anæsthetic. He found considerable difficulty in stopping the bleeding from the small wound, which continued to ooze for several hours. It is remarkable that neither before nor during the subsequent course of the disease was there any sign of spontaneous hæmorrhage. The photo-micrographs shown were taken from slides prepared from the biopsy.

On March 24th a blood-count was made and showed the following: Red cells, 2,035,000; hæmoglobin, 40 per cent.; white cells, 730,000. A differential leucocyte count showed: Polymorphonuclears, 50 per cent.; lymphocytes, 35 per cent. (31 per cent. large and 4 per cent. small); eosinophiles, 2 per cent.; myelocytes, 10 per cent.; eosinophile myelocytes, 3 per cent.; mast-cells, 0·3 per cent. There were two normoblasts and one megaloblast with a mitotic nucleus in 100 white cells counted. For these and the subsequent blood-counts we are indebted to the Director of the Clinical Laboratory, Dr. C. Slater, and to Mr. H. W. Bayly.

Ophthalmoscopically there was slight cupping of the discs but no hæmorrhages. For the first few days after admission the patient felt rather worse, complaining of pain in the back, mostly at nights. On April 5th she did not feel so well as on admission, the appetite was poor, and she had considerable pain in the stomach, probably due to constipation, which required energetic treatment. The spleen was larger than on admission and could be felt below the costal margin. The skin-lesions were practically unchanged, if anything a little paler. On April 16th there was improvement in the general condition and in the blood-count, which was as follows: Red cells, 2,540,000; white cells, 33,640. Differential leucocyte-count: Polymorphonuclears, 70 per cent.; lymphocytes, 18 per cent.; transitionals, 1 per cent.; eosinophiles, 3 per cent.; myelocytes, 8 per cent.; mast-cells, *nil*. Three normoblasts were seen in a count of 100 white cells. Many megaloblasts were seen, and considerable polychromatophilia was noted. This improvement appeared to be due to the action of naphthalene tetrachloride, which was started on April 5th; at any rate the improvement coincided with this treatment. There was no change in the skin condition; the pain in the back is still present at times.

On April 23rd the skin-lesions were flatter and paler on the abdomen, but one or two fresh ones have appeared on the legs and thighs, and some of the old ones in this region have increased a little in size. On April 28th the patient's general condition showed further improvement, the pains were better, she felt stronger and was eating better, but the blood-count did not bear this out, and an interesting change in the relative proportion of leucocytes had taken place, the number of lymphocytes being greatly increased, as follows: Red cells, 2,620,000; white cells, 410,000. Differential leucocyte-count: Poly-

morphonuclears, 48 per cent.; lymphocytes, 48 per cent. (44 per cent. large and 4 per cent. small); eosinophiles, 2 per cent.; mast-cells, 0·5 per cent.; myelocytes, 1·5 per cent. One normoblast was seen in a count of 100 white cells.

The patient was, however, sent to the Atkinson-Morley Convalescent Hospital at Wimbledon, where she remained until May 13th, when she was readmitted into the hospital. The improvement had not continued while at the convalescent hospital, the patient being rather worse in her general condition than when she went away. In addition there was a large sub-periosteal swelling on the right tibia occupying about two thirds of the anterior border; this did not appear to be hæmorrhagic, and was extremely tender to touch. The abdominal skin nodules were fainter in colour but there were many more out on the lower limbs, and those on the thighs had a definite greenish colour.

On May 14th a blood examination showed: Red cells, 2,445,000; white cells, 98,400. Differential leucocyte-count: Polymorphonuclears, 59 per cent.; lymphocytes, 24 per cent. (22 per cent. large and 2 per cent. small); mononuclears, 2 per cent.; transitionals, 5 per cent.; eosinophiles, 1 per cent.; myelocytes, 9 per cent.; mast-cells, *nil*. One normoblast was seen in a count of 100 white corpuscles.

The swelling on the right tibia gradually went down, and on May 20th it was no longer tender; it did not leave any bruising as it disappeared. On May 21st the patient said she felt better, and, at her own request, went to her own home in Pimlico, and could not be persuaded to return to the hospital again.

While she was in the hospital the temperature during the first week showed a slight regular evening elevation (100° F.), being normal in the morning. It then became rather more irregular, and on April 8th reached 101·5° F., which was the highest observed; from that date until she was discharged it was never above 100° F. The urine usually contained crystals of uric acid, and once a trace of albumin, but there was never any hæmaturia. Letters asking her to come up to the hospital for inspection not meeting with success, on August 17th one of us visited her in her home. She was feeling much better and going about a little, but quickly got tired and out of breath on any exertion. The skin-nodules on the trunk were unchanged, but a large one had appeared for the first time on the face, occupying the outer half of the right eyelid.

During September and October we again wrote three times making inquiries without getting any reply; at last we heard from a sister that the patient had died on October 3rd. One of us then visited the sister and obtained the following details: The patient remained fairly well until the end of August, but during the first week in September she suddenly became worse, refusing food and complaining of pain in the stomach, which was swollen. She became rapidly very weak, and the "pain and swelling increased in the stomach, being very bad just before she died." The skin-lesions did not change much during the last few weeks. No post-mortem examination was made.

Treatment: *Soamin.*—On March 23rd the patient was given injections of soamin 1 grain daily, but as it appeared to upset her digestion and cause nausea it was discontinued after a few days.

Naphthalene tetrachloride.—This drug was employed by Drysdale (7) in a case of comparatively acute myelogenous leukæmia with intestinal symptoms, and was followed by remarkably good results, the patient being apparently cured. Impressed with this success, which one of us had an opportunity of seeing, our patient was given naphthalene tetrachloride, at first in 10-grain doses twice a day, and subsequently in 8-grain doses six times daily. She certainly improved very greatly, but as she was for most of the time being treated by X-ray exposures it is impossible to estimate accurately the influence of this drug.

X-rays.—As just mentioned, the patient's improvement while undergoing a course of X-rays was most noticeable; not only did she feel better, but the cutaneous nodules receded and became smaller. Further, she relapsed when she went to the Convalescent Hospital at Wimbledon and when she left the hospital.

Discussion.

Various skin-lesions have been described in connection with leukæmia.

(1) Diffuse œdema-like infiltration, producing in the face, where it is most frequently seen, a leonine expression not unlike that of leprosy. The only sign in our case of this form was the nodule which appeared late in the disease on the right eyelid, and which, although less circumscribed than the other nodules, was hardly diffuse enough to be described as œdema; it was also the same colour as the other nodules. Galliard's (8) case was an example of this leonine infiltration.

(2) Large subcutaneous tumours varying in size from that of a pigeon's egg to that of a fist. Our case showed nothing of this kind. The only case in which ulceration of the growths has occurred is the remarkable example recorded by Sir T. Oliver (14), in which an egg-shaped tumour in the axilla was complicated by necrosis of skin, presumably due to traumatic and infective influences. In this case there were sixty hard tumours, varying in size from that of a bean to that of an egg, scattered over the trunk. The case was remarkable in following a crushing injury to a metacarpal bone, a sequence which naturally suggests a generalised sarcomatosis, but as the leucocytes were enormously increased in numbers it cannot be excluded from the category of leukæmic dermatoses (*leucémides*, Brocq [3]).

(3) Smaller nodules in the skin scattered about all over the body, arranged more or less symmetrically as in our case. The point in which our case appears to be unique is in colour; we have not been able to find any records of this peculiar grey or plum colour. They appeared more commonly to be either brown, yellow, or pink, as in Hochsinger's and Schiff's case (9), and in Phillipert's (15), which, in addition, showed leontiasis, referred to above. Umbilication and bullæ on the nodules have been observed by Lavenson (11), and scaliness by Biesiadecki (2), who in 1876 was the first to describe skin-lesions in leukæmia.

(4) Finally, there has in the past been a considerable amount of confusion, not only between leukæmia and lymphadenoma, but also between their cutaneous lesions. Probably this confusion accounts for the description of the following conditions as the manifestations of leukæmia, namely, prurigo-like papules, lichen-like papules, eczematous conditions, eruptions resembling pityriasis rubra, or general exfoliative dermatitis (Nicolau [13]), all of which are associated with intense pruritus. Although there is hardly sufficient evidence to deny the occurrence of these conditions in leukæmia as apart from lymphadenoma, our impression is that they belong to lymphadenoma and not to leukæmia. Kaposi's lymphodermia perniciosa appears to be generally regarded as allied to mycosis fungoides (5). At one period in the disease the possibility that the condition was chloroma was suggested to us by the green tinge manifested by the lesions on the thighs. It may also be noted that this explanation fitted in more or less with the blood-picture, namely,

increase of lymphocytes, and with the presence of a periosteal swelling, which are commonly seen in chloroma. This disease is very closely related to lymphatic leukæmia, though a few examples of myeloid chloroma have been reported, and is very rare; in 1904 Dock (6) accepted thirty-six cases, and since then Treadgold (17) has collected six more cases, making forty-two in all.

Histology.

The only material available was that taken at the biopsy. This was put through paraffin in the usual manner, cut and stained by the following methods: Borax methylene blue, Jenner's, Leishman's, Giemsa's, and Pappenheim's.

The epidermis was seen to be thin, but not unusually so for the part of the body from which the tissue came. There was some intracellular œdema in the prickle-cell layer due to pressure, otherwise there was nothing abnormal. There was no leucocytic infiltration between the epidermal cells.

The corium and upper part of the subcutaneous tissue showed between the collagen bundles a dense infiltration of cells, which appeared to be lymphocytes and polymorphonuclear leucocytes. The cells were so close together in places as to mask the fibrous tissue supporting them. Where they were not so numerous, near the edges of the infiltration, the cells were chiefly collected around the blood-vessels and lymphatics, and appeared to have exuded from the blood-vessels rather than to have been produced on the spot. Pincus (16), writing on the changes in the skin in leukæmia and pseudo-leukæmia, favours the view that the nodules are derived from the normal lymphatic tissues in the skin, and are not the result of exudation from the blood. He also is of the opinion that the tumour formations in leukæmia and in pseudo-leukæmia are indistinguishable; in our case the entire absence of the appearances, which have since been shown by Andrewes (1) to be characteristic of lymphadenoma, together with the clinical signs, eliminate that diagnosis.

The section stained by Pappenheim's method showed a complete absence of plasma-cells; this is opposed to Unna, who speaks of these nodules as a "special form of granuloma."

The section stained by borax methylene-blue showed a few mast-

cells, which have also been noted in lymphadenoma by Dr. Graham Little (11).

It is very greatly to be regretted that we were unable to get a necropsy and so give a more complete account of the pathology of the case.

Remarks on the Form of Leukæmia in this Case.

As it is usually considered that cutaneous tumours in leukæmia are almost exclusively confined to the lymphocytic form, and as Cabot (4) states that their occurrence has not been recorded in myeloid leukæmia, it is important to call attention to the condition of the blood in this case. It was not a characteristic example of lymphoid leukæmia, for the highest lymphocyte-count was 48 per cent. in contrast to an average of 90 per cent. in typical cases. The highest percentage of myelocytes was 10 per cent. and the lowest 1·5 per cent., so that the case is certainly not characteristic of ordinary myeloid leukæmia. Muir (12) admits that in lymphoid leukæmia small numbers of myelocytes may appear in the blood as the result of nodules in the bone-marrow. But inasmuch as 90 per cent. of the lymphocytes were of the large form, and may be regarded as the non-granular precursors of the myelocytes (Muir), this case obviously belongs to the category of myeloid rather than of lymphocytic leukæmia. Cases with a blood-count resembling that in our case have been described as "mixed leukæmia," but as Cabot in a series of 140 cases of leukæmia did not find any example deserving this description in the strict sense of the term, and further, as it has in the past been applied to cases of ordinary myeloid leukæmia, it appears better to be content with calling the condition "atypical myeloid leukæmia." The relation of this case to chloroma has already been raised, but the discussion of this question is rendered almost futile by the absence of a necropsy. The only reason for thinking of this rare condition was the greenish tint of some of the cutaneous nodules and the presence of what appeared to be a subperiosteal growth; as far as we know, chloromatous invasion of the skin has not been reported.

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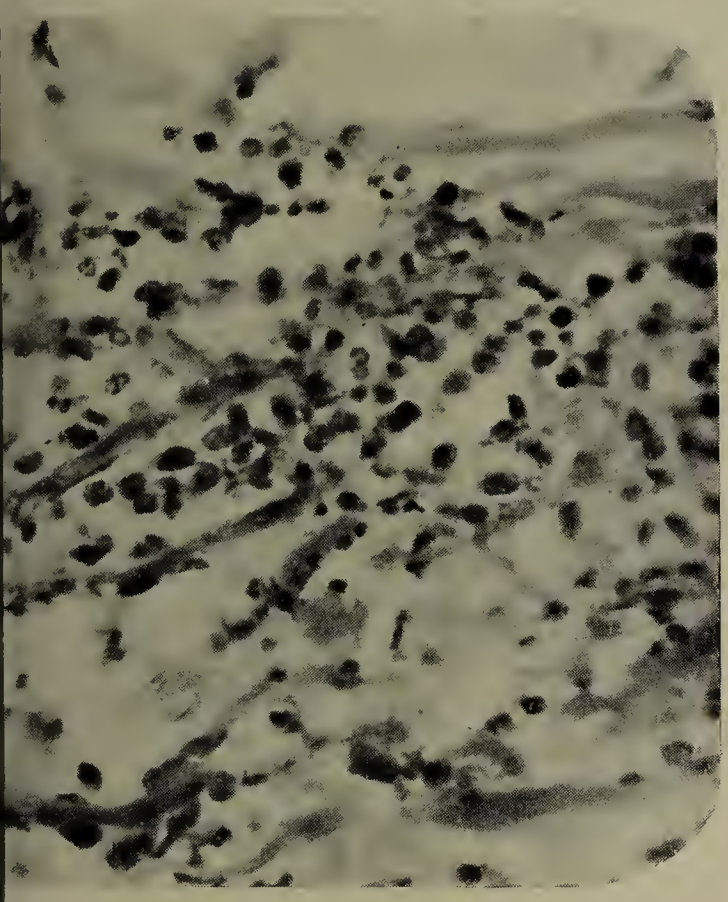

crograph of leukæmic nodule in the skin. High power.

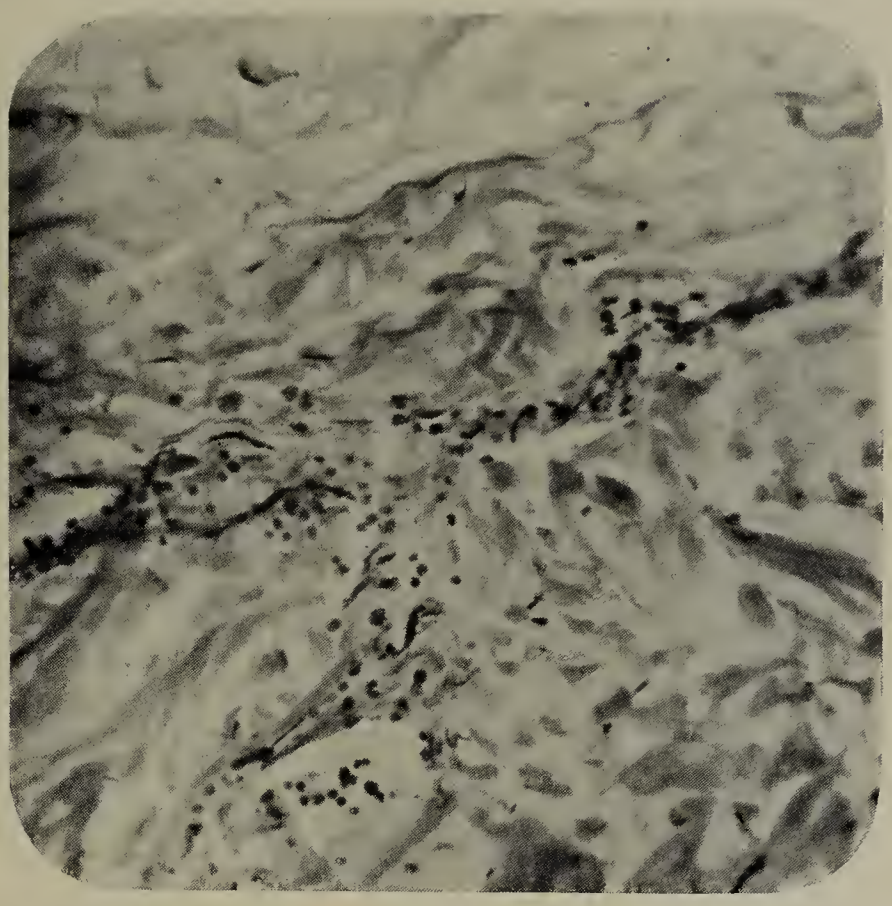

Photo-micrograph of skin at the margin of a leukæmic nodule; shows perivascular exudation of lymphocytic cells. High power.

icrograph of leukæmic nodule in the skin. High power.

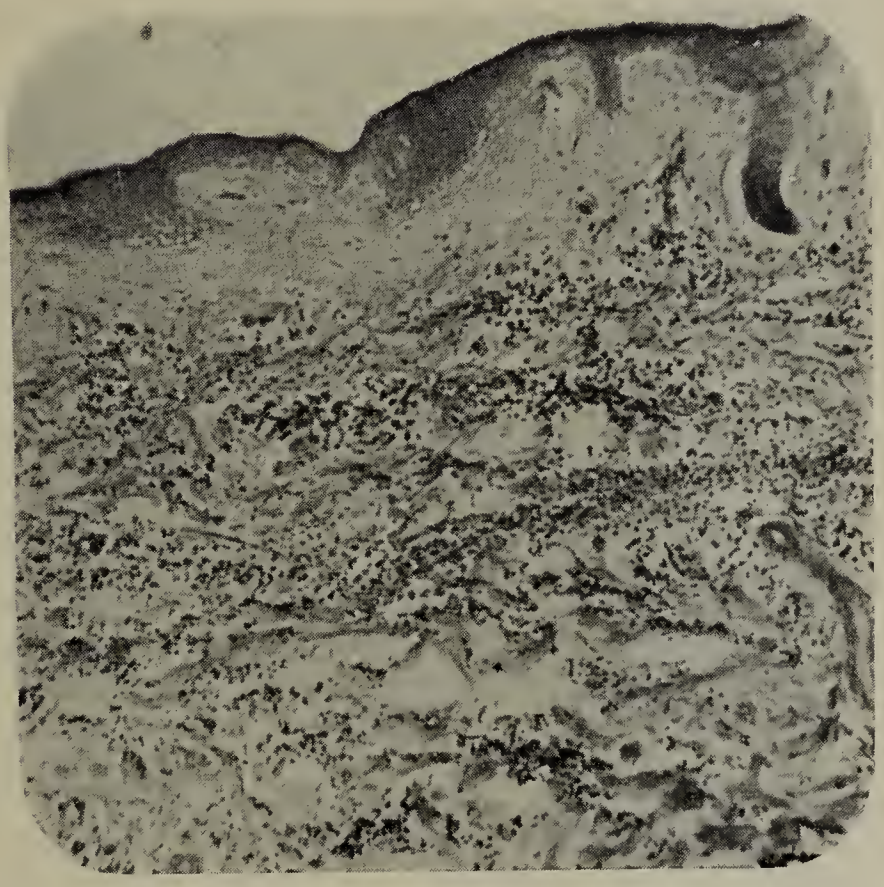

Photo-micrograph of leukæmic nodule in the skin. Low power.

LUSTRATE THE PAPER ON ATYPICAL MYELOID LEUKÆMIA WITH NODULAR INFILTRATION OF SKIN (H. D. ROLLESTON AND WILFRID FOX).

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